Contraception, hormone replacement therapy and thrombosis

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SYNOPSIS

The combined oral contraceptive pill and hormone replacement therapy increase the risk of venous thrombosis. Women should be checked for other factors predisposing them to thrombosis before these drugs are prescribed. The increased risk is usually attributed to oestrogen. Case-control studies of patients taking contraceptives containing the progestogens desogestrel, gestodene or norgestimate, suggest these drugs may also increase risk. However, confounding factors in these studies make interpretation difficult. The increased risks associated with hormone replacement therapy may be offset by its benefits in relieving menopausal symptoms.

Index words: desogestrel, gestodene.

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Introduction

In healthy young women the estimated incidence of venous thromboembolism is one per 10 000 woman years of follow-up. The association of combined oral contraceptives with an increased risk of venous thromboembolism has been documented since the 1960s. There are no reliable data suggesting that progestogen-only methods carry an increased risk of venous thromboembolism, but some studies suggest the newer progestogens used in combined pills may increase the risks. Women taking hormone replacement therapy (HRT) also have an increased risk of thromboembolism.

Risk factors for venous thromboembolism

Venous thromboembolic disease manifested either as a deep vein thrombosis or a pulmonary embolus is rare amongst young women but increases with age. Other factors associated with an increase in venous thromboembolism include obesity, smoking and inherited thrombophilia. The risk of venous thromboembolism increases following surgery, trauma, immobilisation, during and immediately following pregnancy, in cancer patients, during long-distance air travel and with the use of combined oral contraceptives (Table 1). Other conditions which are associated with an increased risk of venous thromboembolism are autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease, hypothyroidism and renal disease.

Venous thromboembolism and combined oral contraceptives

A number of changes occur in the complex pathways of coagulation and fibrinolysis in women using combined oral contraceptives. These include a significant increase in fibrinogen and vitamin K-dependent coagulation factors, but there is also a significant increase in fibrinolysis which may balance any potential thrombotic risk in women without other risk factors for venous thromboembolism.

The risk appears to be related to the oestrogen dose. As the oestrogen dose has been reduced, the incidence of venous thromboembolism has declined from 9–10/10 000 woman years for high-dose oestrogen pills (≥ 50 microgram) to 3–4/10 000 woman years for low-dose (≤ 35 microgram) pills.

The progestogen question

In 1995 the British Committee on Safety of Medicines (CSM) issued a warning about a reported increased risk of venous thromboembolism in women taking combined oral contraceptives containing the ('third generation') progestogens desogestrel, gestodene or norgestimate compared to those containing levonorgestrel or norethisterone ('second generation').[1] As a result a large number of women taking third generation pills either changed to other formulations or discontinued use of oral contraceptives. There was a subsequent increase in unplanned pregnancies and induced abortions.[2]

Table 1

Risk of thromboembolism in women taking oral contraceptives according to personal characteristics

Characteristic	*No combined oral contraceptive*	*Taking second generation oral contraceptive*	*Taking third generation oral contraceptive*
Non-smoking, no risk factors	5–11/100 000	9–19/100 000	30/100 000
Hereditary thrombophilia	67/100 000	215/100 000	431/100 000
Current smoking	14/100 000	N/A	N/A
BMI > 30	20/100 000	N/A	N/A

Attributable risk factors for venous thromboembolism with obesity and smoking in women taking second and third generation pills are not available. In women taking a combined oral contraceptive, those with a BMI > 25 have an odds ratio of 6.4 for venous thromboembolism compared to women with BMI < 20. Attributable risk also increases with age.

Assessing the evidence

The CSM's advice was based on case-control studies published in 1995–96 which suggested that the odds ratios for venous thromboembolism in women taking combined oral contraceptives containing desogestrel, gestodene or norgestimate were 1.5–2.3 compared to combined oral contraceptives containing levonorgestrel and norethisterone.[3,4,5] Publication of these studies was followed by a number of articles pointing out possible sources of bias[6], the lack of a plausible biological explanation for the findings and a number of confounders that were not identified or taken into account in the original studies.

Prescribing bias

Bias occurs when a drug is prescribed more commonly to women with a medical condition that could be a contributory cause to the condition under scrutiny. Analysis of the studies showed that second and third generation combined oral contraceptives tended to be used in different populations of women. As third generation progestogens were less androgenic and considered to carry even less cardiovascular risk than low-dose second generation pills they tended to be prescribed more commonly for women with cardiovascular risk factors.[7]

Healthy user effect

This refers to how the duration of use influences the characteristics of the user population. Venous thromboembolism usually occurs in the first year of taking a combined oral contraceptive particularly in women with risk factors. As second generation pills have been marketed for much longer (than third generation pills) women with venous thromboembolism would have already stopped using them, leaving a group of continuing users who were at lower risk of venous thromboembolism. The early studies of users of second generation pills showed a risk ratio of 3.9 whereas the 1995–96 studies of the same pills showed the highest risk ratio to be 1.6 compared to non-users. In addition to having taken their pills for a shorter duration, prescribing bias added to the risk because third generation pills were more likely to be prescribed for women with cardiovascular risk factors. (There were preliminary data to suggest that women taking third generation pills were less likely than women taking second generation pills to have a myocardial infarction.[8]) The risk factors of the two groups were therefore not comparable.[7]

Confounders

A confounder is a characteristic of the user, which distorts the risk associated with exposure to a particular therapy because in itself it could increase the risk of the condition under scrutiny. The three original studies adjusted for possible confounders such as body mass and age but not for duration of use.[3,4,5] When first-year users of third generation pills were compared with first-year instead of long-term users of second generation pills, there was no significant difference in the incidence of venous thromboembolism (odds ratio 1.4, 95% confidence interval (CI) 0.8–2.5).[9]

In 1998 two further case-control studies used separate general practice populations and tried to avoid some of the deficiencies and address some of the criticisms of the earlier studies. They found no significant difference in the risk of venous thromboembolism between second and third generation combined oral contraceptives[10], while a third study appeared to confirm the risk, adding to the debate and confusion.[11]

What does the evidence mean?

Until the CSM's warning no previous association had been demonstrated between progestogen potency and venous thromboembolism. Furthermore a review of all 17 comparative studies on the haemostatic effects of desogestrel, gestodene and levonorgestrel-containing combined oral contraceptives found no difference in the established risk markers for venous thromboembolism between the third and second generation products.[12]

In 1998 the World Health Organization reported that combined oral contraceptives containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that of combined oral contraceptives containing levonorgestrel. However, thromboembolism is so rare that their increased risk contributes very little to the mortality or long-term disability of oral contraceptive users.[13]

Although the debate about the differential risks of second and third generation combined oral contraceptives continues, the absolute risk of deep vein thrombosis in young women without risk factors for venous thromboembolism is extremely low. However, a low risk of venous thromboembolism may outweigh any advantages third generation pills have over second generation pills.

Prescribing steroidal contraception

When prescribing contraception a careful medical history must be taken to exclude either a personal or strong family history of thromboembolic disease and risk factors for venous thromboembolism. Women with no risk factors for venous thromboembolism may be prescribed any combined oral contraceptive containing 35 microgram or less of ethinyloestradiol. However, they should be informed of the controversy surrounding third generation progestogens and given a choice of pill formulation based on an assessment of their individual benefits and risks.[14] Pills containing ethinyloestradiol 50 microgram should only be used if cycle control is an ongoing problem with lower doses.

Women with a confirmed history of a venous thromboembolic episode should never be prescribed the combined oral contraceptive. Those with a strong family history of venous thromboembolism should undergo screening to exclude thrombophilia before starting a combined oral contraceptive. Women with thrombophilia or multiple risk factors for venous thromboembolism should not use combined oral contraceptives. They can use progestogen-only methods, for example the progestogen-only pill, the injectable contraceptive formulation of medroxyprogesterone acetate, the sub-dermal etonogestrel implant, or the levonorgestrel-releasing intrauterine system. Alternatively they could consider use of a copper-bearing intrauterine device or barrier methods.

Danish population studies have shown that non-smoking women over 40 years old have a 10-fold increase in the risk of developing a venous thromboembolism compared to women in their 20s. Obesity further increases the risk. A BMI greater than 30 is associated with an independent risk ratio of 2.27 (CI 1.80–4.11) and current smoking with a risk of 1.42 (CI 1.12–1.79). The more risk factors for thromboembolism the greater the risk of developing a thrombosis while taking combined oral contraceptives.

To minimise the risk of venous thromboembolism, women undergoing pelvic surgery or procedures requiring extensive immobilisation, including wearing a long leg plaster, should, wherever possible, stop combined oral contraceptives two to four weeks before the procedure. They should not resume their pill until two weeks after achieving complete mobilisation. Alternative methods of contraception should be used during this period and should be started as soon as the pill is discontinued. In women who are not breastfeeding the combined oral contraceptive should not be started until three weeks postpartum.

Hormone replacement therapy and thromboembolism

Hormone replacement therapy appears to be related to an increased risk of venous thromboembolism in the first 12 months of use. The estimated incidence of idiopathic thromboembolism in postmenopausal women not using HRT is estimated to be 13/100 000 women, while in women using HRT it is 20–30/100 000. A large population-based study has found the adjusted odds ratio in HRT users compared with non-users was 4.6 (CI 2.5–8.4) in the first six months of use and 3.0 (CI 1.4–6.5) 6–12 months after starting treatment.[15] No major differences in risk were observed between users of high and low oestrogen doses, unopposed or opposed oestrogen treatment, and oral or transdermal therapy. Among current users of HRT, idiopathic venous thromboembolism occurs at two to three times the rate in non-users accounting for one to two additional cases per 10 000 women, per year.

Given the benefits of HRT in relation to relief of menopausal symptoms, a small increase in the risks of venous thromboembolism may be an acceptable trade-off for many women. However, it is important that women are informed of the slightly increased risk of venous thromboembolism to enable them to make an informed decision about taking HRT.

Conclusion

All women should be given information about the (low) risk of venous thromboembolism with combined oral contraceptive use and advised under what conditions to stop the pill and switch to alternative methods of contraception. The benefits of HRT on menopausal symptoms also greatly outweigh the risk of venous thromboembolism for women without risk factors.

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 75)

3. As the risk of thrombosis is low, women do not have to stop taking the combined oral contraceptive pill before elective surgery.
4. The low dose of oestrogen used in hormone replacement therapy is not associated with an increased risk of venous thromboembolism.